April 9, 2002

Dr. Lisa Navarro
Cytec Industries Inc.
Corporate Headquarters
Five Garret Mountain Plaza
West Paterson, NJ 07424

Dear Dr. Navarro:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 2-hydroxy-4-n-octoxybenzophenone, posted on the ChemRTK HPV Challenge Program Web site on November 14, 2001. I commend Cytec Industries Inc. and Ciba Specialty Chemicals Corporation for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its HPV Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the attached Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Cytec Industries and Ciba Specialty Chemicals Corporation to advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
2-Hydroxy-4-n-Octoxybenzophenone

The sponsors, Cytec Industries, Inc. and Ciba Specialty Chemicals Corporation, submitted a test plan and robust summaries to the EPA for 2-hydroxy-4-n-octoxybenzophenone (CAS No. 1843-05-6) dated October 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on November 14, 2001.

SUMMARY OF EPA COMMENTS

1. Physicochemical and Environmental Fate Data. EPA agrees with the Test Plan and Robust Summaries for these endpoints. The submitters need to clarify the method used for the biodegradation test.

2. Health Endpoints. The submitters= plan to conduct no further testing for acute toxicity, repeated-dose toxicity, and genetic toxicity is acceptable. EPA recommends that a reproductive/developmental toxicity test (OECD 421) be performed. The available study used a dose level that was significantly lower than the guideline-recommended limit dose.

3. Ecotoxicity. Because this chemical has a high Log K_{ow}, a chronic daphnia test is recommended. The submitters should also conduct an acute test in algae because the submitted test was inadequate due the use of a dispersant.

EPA requests that the Submitters advise the Agency within 60 days of any modifications to their submission.

EPA COMMENTS ON 2-HYDROXY-4-n-OCTOXYBENZOPHENONE CHALLENGE SUBMISSION

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The submitters' approach to these endpoints is acceptable for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, transport/distribution)

The submitters' approach to these endpoints is acceptable for the purposes of the HPV Challenge Program. However, the submitter needs to clarify the method used for the biodegradation test (see Specific Comments on the Robust Summaries).

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for acute toxicity, repeated-dose toxicity, and genetic toxicity; however, data for reproductive/developmental toxicity are inadequate and additional testing should be performed for this endpoint.

Acute Toxicity. The submitted oral study, conducted prior to the establishment of GLP and OECD guidelines, used only male rats and had an observation period of only 7 days. However, these are minor deficiencies, since the tested dose was 10 g/kg (5 times higher than recommended for limit tests), and no deaths, adverse clinical signs, or abnormalities at necropsy were observed.

Repeated Dose Toxicity. Although all of the studies predated GLP and OECD guidelines, four submitted oral (dietary) toxicity studies in rats (one 30-day and three 90-day studies) provide adequate information on repeated dose toxicity (oral). One of the 90-day studies (study C) did not report any toxicity, but this result was consistent with the dose-response relationships reported in the other rat studies.

Reproductive and Developmental Toxicity. The submitters conclude that no further testing for these endpoints is needed because there is a 4-generation dietary study in rats. However, this study (which pre-dated GLP and OECD guidelines) does not appear to be adequate because it used a single dietary level (0.6% or 6000 ppm) that was considerably below the limit dose (1000 mg/kg/day or 20,000 ppm in the diet) recommended by both EPA and OECD test guidelines.

Genetic Toxicity. One study (B) of genetic mutation in bacteria and a GLP study of chromosomal aberration in human lymphocytes (conducted under OECD guideline 473) adequately address the genetic toxicity endpoint.

Ecotoxicity

The submitters should conduct a daphnid chronic reproductive toxicity test because this chemical has an estimated Log K_{ow} greater than 6.0 and chronic testing is appropriate for chemicals with Log K_{ow}s of greater than 4.2. In addition to the chronic test, the submitters need to conduct an acute test in algae. The submitted algae test was inadequate because the use of a dispersant could understate the toxicity of this chemical.

To test this chemical, the submitters need to follow the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (available at http://www.oecd.org/ehs/test/monos.htm). Additional guidance for acute and chronic testing of low water solubility chemicals of this type can be found in the Federal Register (at 65 FR 81695). The web address is http://www.epa.gov/fedrgstr/EPA-TOX/2000/December/Day-26/t32498.htm.

Specific Comments on the Robust Summaries

Environmental Fate

Biodegradation. On page 16 of 38 of the Robust Summary, under Biodegradation, the submitters indicate that the method used is OECD Guideline 301B and notes that the title is the algae growth inhibition test. This statement is incorrect because OECD Guideline 301B is the CO_2 Evolution or Modified Sturm Test, which is a test of ready biodegradability of non-volatile substances in an aerobic aqueous medium. The algae growth inhibition test (OECD guideline 201) is unrelated to OECD Guideline 301B. The submitters need to reference correctly the method used to measure biodegradation.

Health

Acute Toxicity. The submitters need to add the following information to the robust summary: the purity of the test material, the method of administration, and body weight data.

Repeated-Dose Toxicity. Robust summaries for repeated-dose oral toxicity were incomplete, but provided sufficient information to evaluate the studies. For all summaries, the submitters need to provide data on the stability of the test material in feed and explicitly state NOEL/NOAELs and LOEL/LOAELs and doses in terms of mg/kg body weight for each sex. Additional comments on individual studies are as follows:

> For the summary of the 30-day study (A) in rats, the submitters should add the purity of the test material and the incidences of clinical signs and renal histopathology by dose level.
>
> For summary (B), it would be useful for the submitters to add a list of organs that were examined for microscopic pathology, since the summary notes that extensive examination was done.
>
> For the summaries of two 90-day studies (C and D) in rats, the submitters need to report the purity of the test material. A list of the organs that were weighed or examined for gross and microscopic pathology would also be useful for a complete evaluation of these studies.

If the 120-day study (E) in dogs is to be used as supporting information for this endpoint, the submitters should include more discussion of the actual dose level of the test material (due to food refusal in the high-dose group and other selected animals). Also, the reliability of this study is suspect due to the following problems: small group sizes (2/sex), occurrence of parasitic intestinal infestation in some dogs (group not reported), a jaw abnormality that reduced feed intake in one female, and the absence of a level producing exposure-related adverse effects. Therefore, the reliability code of 2e should be changed to 3b (significant methodological deficiencies).

Genetic Toxicity. The submitters need to characterize the identity of the test material in all three genetic toxicity summaries.

The summary for one study of bacterial genetic mutation (study (B)) was adequate (except for the need for purity information). However, if study (A) is to be used as support for study (B), additional details are needed to make a complete evaluation of the study. Specifically, the submitters need to report the concentration levels, the cytotoxic concentration, and the identity of "ATK 1050" mentioned in the "Results" for study (A).

Followup Activity

EPA requests that the Submitters advise the Agency within 60 days of any modifications to their submission.